

REMARKS

Claims 1-35 are pending. Claims 30-35 are withdrawn following restriction of the application.

Claims 1 and 16 are amended herein to correct a typographical error noted by the Examiner. The term “polyethylenimine” is now spelled consistently throughout the application.

Claim 1 is also amended to recite that each cyclodextrin moiety in the polymer is attached to one or two polyethylenimine (PEI) moieties and not to any cyclodextrin (CyD) moiety. Support for this amendment is provided in the specification in that CyD contains numerous hydroxyl groups, but contains no amine groups. On the other hand, PEI contains no hydroxyl groups but many amine groups. The linker used in the working examples (carbonyldiimidazole, CDI - see, e.g. Figure 1A and page 6, line 20) can interact with one hydroxyl group and one amine group, but not two hydroxyl groups or two amine groups (see, e.g. <http://en.wikipedia.org/wiki/Carbonyldiimidazole>). Since CyD contains only hydroxyl groups and PEI contains only amine groups, there can be no CyD-CyD or PEI-PEI formed.

The Examiner's definitions for the purpose of prosecution

Applicants disagree with the Examiner's interpretation of the claims that “copolymer”s of the invention can include branched polymers. The present claims include a recitation, “wherein the cyclodextrin is modified at no more than two positions by an activating agent to allow attachment to no more than two polyethyleneimine molecules.” This recitation expressly precludes any branching of the polymers. As explained previously, if each CyD has only two activated sites that only bound polyethylenimines (PEIs), then the copolymers in the present invention cannot be branched polymers or grafted polymers. Neither can they be block copolymers, except PEI-CD block copolymers.

The Examiner appears to have ignored this recitation in the claims. Applicants submit that the Examiner must include it in his considerations of the scope of the claims.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 1-2 and 5-15 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner alleges that the specification does not provide support for the claimed limitation “modified at no more than two positions.” The Examiner contends that Fig. 1 alone does not satisfy the written requirement. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The specification actually contains additional support for the recitation of, “wherein the cyclodextrin is modified at no more than two positions by an activating agent to allow attachment to no more than two polyethyleneimine molecules.” First, Applicants refer to the copolymer in the present invention as “PEI-CyD copolymers”, which suggests PEI-CyD block copolymers. See page 9, line 1-2, page 10, line 30, and page 11, lines 7. Second, applicants explicitly disclose on page 10, lines 14-16, that for a linear structure copolymer to be obtained, the β -CyD with modification degree of 33% was used for the reaction with PEI. Third, in the “Summary” section, applicants disclose that “Activated β -cyclodextrin was reacted with low-Mw PEI to form linear structure of PEI-CyD.” Thus specification thus contains ample support for a linear copolymer.

Furthermore, in Fig 2 CyD(DMSO) and CyD(D₂O) show the ¹H NMR spectra of β -cyclodextrin in DMSO and D₂O. The data show all active protons of CyD appearing in DMSO and that only some protons are replaced in D₂O. Hence, the hydroxyl groups attached to carbons 2, 3 inside the ring of CyD were assigned to peaks at δ 5.6-5.8 ppm, the carbon 6 hydroxyl group corresponds to the peak at δ 4.5 ppm, and the carbon 1 hydrogen corresponds to the peak at δ 4.8 ppm. To prepare activated CyD, different amounts of CDI were tried. In Fig. 3, with the increase in the amount of CDI, the peak at 4.5 ppm was decreased, indicating decrease in the protons from C6 hydroxyl group of the β -cyclodextrin ring due to reaction with CDI. The ratios could be calculated according to the integral values obtained from the numbers of the H proton of CyD in C1 and OH proton of CyD in C6 in NMR spectra. In an attempt to synthesize a linear structure polymer, only 33% of hydroxyl groups in the ring of CyD were modified, which correlates to 2 of hydroxyl groups per each CyD that were activated and react with the amine

groups of PEI. This is experimental evidence that supports the claim term that the polymer is “modified at no more than two positions.”

The conclusion of the linear copolymer structure, i.e. one in which the cyclodextrin is modified at no more than two positions, is further supported by Fig. 4. In the case of the ¹H NMR spectra of PEI600 and PEI600-CyD, the peaks at δ 2.3-2.8 ppm were assigned to protons of -CH₂-CH₂-N from PEI600. Stoichiometry calculated from the characteristic peaks of PEI600 (CH₂CH₂NH-) and C-1 hydrogen of CyD indicates clearly the molar ratio of 1:1 between PEI600 and CyD in the copolymer with molecular weight of 63 kDa.

Together with Figure 1, showing a linear polymer with modification of only two positions of the cyclodextrin, Applicants submit that the specification provides ample evidence that the Inventors had indeed invented a polymer in which “the cyclodextrin is modified at no more than two positions by an activating agent to allow attachment to no more than two polyethyleneimine molecules.” That is all that is necessary to establish sufficiency of the written description of the specification. *Vas-Cath v. Mahurkar*, 19 USPQ2d 111 (Fed. Cir. 1991). Accordingly, the instant rejection should be withdrawn.

Rejections under 35 U.S.C. §103

over Kosak et al. and Davis et al.

The Examiner has rejected claims 1-2, 5-9, 11-12, 16-18, 21-25, and 29 under 35 U.S.C. §103(a) as being unpatentable over Kosak et al. (US Pat. Pub. 2001/0034333, hereinafter “Kosak ‘333’”) and Davis et al. (US. Pat. 6,509,323, hereinafter “Davis ‘323’”). This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Applicants first note that this rejection is based on the alternate reading of claims 1 and 16 that the copolymer contains alternate monomer units of PEI-CyD-PEI-CyD or PEI-PEI-CyD-CyD.

The Examiner asserts that Kosak ‘333 teaches the incorporation of PEI into CyD polymers. The CyD molecules in Kosak ‘333 are selected from a group consisting of CyD derivatives, oxidized CyDs, CyD dimers, CyD trimers, and CyD polymers. Kosak ‘333 fails to disclose a PEI-CyD block copolymer that has a linear structure. Kosak ‘333 only discloses biocleavable linkage

among CyD polymer carriers but not between CyDs and PEIs. The Examiner concedes that Kosak '333 does not teach that the PEI and CyD copolymer is a linear polymer, nor that the CyD is modified at no more than two positions by an activating agent to allow attachment to no more than two PEI molecules.

In fact, the incorporation of PEI into the CyD polymers of Kosak is not within the "backbone" of the polymer as in the present invention, but rather by derivitization of the hydroxyls of the CyD such that the PEI molecules are pendant from the CyD polymer as "side chains". Applicants note that all of the disclosure of Koszak '333 pointed out by the Examiner relates to such embodiments. This fact evidences that the Examiner's assertion of *prima facie* obviousness is merely hindsight picking and choosing of claim elements from the prior art and their combination using the present claims as template. Such an approach to asserting obviousness has been continually rebuked by the Courts and is improper.

The Examiner then attempts to cure these deficiencies of Kosak '333 with Davis '323.

Applicants submit that Davis '323 does not cure the many deficiencies of Kosak '333. The linear CyD copolymer in Davis '323 has a repeating unit of formula Ia and Ib, shown on column 4. The linear copolymer disclosed in Davis '323 thus consists of CyD and comonomer A that can covalently bond to another CyD. The PEG diacid chloride in Example 12 simply serves to link CyDs and it does not play a role in the alleged function of delivery of therapeutic compounds. The presence of ester groups and a polyethylene structure is only incidental. The argument that PEG is structurally similar to PEI so it offers teachings pertinent to the present invention is simply based on impermissible hindsight as explained above. This is evidenced, for example, by the Examiner's confusing a reactive monomer A that "upon reaction with a cyclodextrin monomer ... linked two cyclodextrin monomers together", with the fact that in making the polymer of the instant invention, the cyclodextrins are first reacted with CDI before reacting with PEI. PEI itself is not reactive with CyD. In this regard, Applicants further note that PEI is not among the "monomer A" structures recited by Davis '323. See, col. 7, line 24 through col. 8.

Claim 1 is amended herein to recite more expressly that the polymer does not include Cyd-Cyd blocks, and this more clearly distinguishes the invention from what is disclosed by Kosak '333 and by Davis '323. Applicants take due note that the Examiner admits that the rejection is based on

a claim interpretation that includes blocks of CyD interrupted by one or more PEI units. Such arrangement is now expressly excluded from the claims.

As explained above, the instant invention is not *prima facie* obvious over the combination of Kosak '333 with Davis '323. Accordingly, the instant rejection should be withdrawn.

Over Kosak et al. and Davis et al. in view of Cheng et al.

Claims 10, 13-15 and 26-28 are rejected under 35 USC § 103(a) as being unpatentable over Kosak '333 and Davis '323 in view of Cheng et al. US 2004/0077595 (hereinafter Cheng '595). This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The Examiner also explains that claims 19 and 26-28 describe a method for synthesizing a biodegradable copolymer comprising certain steps. However, no separate rejection of these claims is set forth. Applicants suppose that claim 19 was intended to be included in the above rejection.

As a threshold matter, the Examiner indicates that the present rejection is based on a claim interpretation that the claims encompass polymers of the PEI-PEI-CD-CD-PEI-PEI-CD-CD form. As explained above, the claims did not encompass such polymers, and further amendments herein clarify that such is the case.

Second, all of the claims noted under this rejection are dependent ultimately from either of claim 1 or claim 16. As explained above, the combination of Kosak '333 with Davis '323 fails to establish *prima facie* obviousness of the presently claimed invention. Cheng '595 does nothing to cure the deficiencies of Kosak and Davis in establishing obviousness of the present invention as described in claims 10, 13-15, 19 and 26-28.


It is very apparent that Cheng '595 relates to branched polymers. This is evident merely from examination of formulae (I), (II) and (III) of the reference. Thus, Cheng '595 expressly teaches away from the present invention, which due to the features described in claim 1 is a linear polymer. Furthermore, formula (III) of Cheng '595 shows a central CyD molecule having four "linker" groups; this embodiment includes linkages in excess of two to the CyD molecule, as recited in the present claims.

Thus, the combination of Kosak '333, Davis '323 and Cheng '595 fails to establish *prima facie* obviousness of the present invention, and the instant rejection should be withdrawn.

In view of the above amendment and remarks, Applicants believe the pending application is in condition for allowance. Such favorable action is respectfully requested.

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Respectfully submitted,

By 
Mark J. Nuell
Registration No.: 36,623
BIRCH, STEWART, KOLASCH & BIRCH, LLP
12770 High Bluff Drive
Suite 260
San Diego, California 92130
(858) 792-8855
Attorney for Applicant